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| Inventors: | **Roger S. Cubicciotti** |
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| Examiner: | **Ware, Todd** |
| Group Art Unit: | **1615** |
| Title: | **Prodrug Compositions and Drug Delivery Methods Using Synthetic Receptors** |

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Dear Sir:

# APPEAL BRIEF

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Appendix I - Rejected claims on Appeal

Appendix II - Pending claims with proposed amendments

## I. Real Party in Interest

The real party in interest of this Appeal is the Assignee of the above-referenced patent application, Molecular Machines, Inc.

## II. Related Appeals and Interferences

The appellant, the appellant's legal representative, and the assignees are not aware of any other appeals or interferences which will directly affect or be directly affected by or have a bearing on the Board's decision in the instant appeal.

## III. Status of the Claims

Claims 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, and 29 are canceled.

Claims 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40 and 41 are pending.

Claims 30, 31, 32, 33, and 41 have been withdrawn from consideration.

Claims 34, 35, 36, 37, 38, 39 and 40 are rejected.

## IV. Status of Amendments

The Amendment filed by Appellant on December 23, 2002 was denied entry by the Examiner.



## V. Summary of the Invention

The claimed invention relates to methods for producing prodrug and multi-prodrug complexes as well as prodrug and multi-prodrug complexes produced by these methods, including immobilized prodrug

and multi-prodrug complexes. In these methods, a drug is first identified. A synthetic receptor for the drug that specifically binds the drug via a saturable, noncovalent interaction between the drug and the synthetic receptor that can be competitively inhibited by structural analogs of the drug is then selected. The synthetic receptor is selected from the group consisting of antibodies, antibody fragments, oligonucleotides and oligosaccharides. In some embodiments, the method further comprises attaching the prodrug or multi-prodrug complex to a biologic or biocompatible structure.

The scope of the drugs that can be used in the methods and complexes of the present invention is described at page 7, lines 14-22, of the specification.

Synthetic receptors and methods for their selection are described at page 9, line 28, through page 10, line 25, of the specification.

Specific binding of the identified drug to the selected synthetic receptor is described at page 7, lines 31-35, of the specification.

Attachment of the prodrug or multi-prodrug complex to a biologic or biocompatible structure is described at page 10, lines 26 through page 11, line 4.

## VI. Issues

The first issue on Appeal is whether claims 34, 35, 36, 37, 38, 39 and 40 are unpatentable under 35 U.S.C. 102(b) as being anticipated by Morgan Jr. et al. (U.S. Patent 5,106,951).

The second issue on Appeal is whether claims 34, 35, 36, 37, 38, 39 and 40 are unpatentable under 35 U.S.C. 103(a) as being obvious in light of Morgan Jr. et al. (U.S. Patent 5,106,951).

## VII. Grouping of Claims

Claims 34, 35, 36, 37, 38, 39 and 40 stand or fall together on the issue of novelty under 35 U.S.C. 102(b).

Claims 34, 35, 36, 37, 38, 39 and 40 stand or fall together on the issue of obviousness under 35 U.S.C. 103(a).

## VIII. Arguments

Claims 34, 35, 36, 37, 38, 39 and 40 stand rejected under 35 U.S.C. 102(b) as being anticipated or rendered obvious by Morgan Jr. et al. (U.S. Patent 5,106,951).

The instant application was filed in October of 1998 and Morgan, Jr. et al. (U.S. Patent 5,106,951) was first cited as a prior art reference by the Examiner in the Office Action of May 23, 2000. Appellant disagreed with the Examiner's characterization of the teachings of Morgan Jr. et al. (U.S. Patent 5,106,951) in the May 23, 2000 Office Action as well as all subsequent Office Actions since that time.

However, pending claims 30-41 were not presented to the Examiner for consideration until November 2, 2001. In the November 2, 2001 amendment, Appellant canceled all pending claims and represented the subject matter in new claims 30-41. These amendments were made in response to suggestions during a Telephone Interview conducted on August 22, 2001 and subsequent telephone discussions thereafter on September 10, 2001 and September 11, 2001 with the Examiner and supervisory Examiner Kishore, to include additional language in the claims relating to the steps by which elements of the claim are selected to assist the Examiner in more effectively searching the instant invention.

Despite this effort by Appellant to facilitate more effective searching by the Examiner, Morgan Jr. et al. (U.S. Patent 5,106,951) was still cited as the only prior art reference against the new claims. For conciseness in this Appeal Brief, it is the Examiner's characterization of Morgan, Jr. et al. (U.S. Patent 5,106,951) with respect to these new claims only which is addressed herein.

The Examiner suggests that the antibody-csDBM of Morgan meets the "antibody fragment" limitation of claims 34, 35, 36, 37, 38, 39 and 40 and therefore anticipates or renders obvious the claims.

**A. Rejection of claims 34, 35, 36, 37, 38, 39 and 40 under 35 U.S.C. § 102(b)**

Claims 34, 35, 36, 37, 38, 39 and 40 remain rejected under 35 U.S.C. § 102(b) as being anticipated by Morgan Jr. et al. (U.S. Patent 5,106,951). The Examiner suggests that the antibody-csDBM of Morgan Jr. et al. is considered to meet the "antibody-fragment" limitation of the instant claims, since no language excluding the csDBM of Morgan Jr. et al. is included in the claims.

Appellants respectfully disagree.

**1. To anticipate a claim, the reference must teach every element of the claim**

In accordance with MPEP § 2131 and the holdings of the Court of Appeals for the Federal Circuit in *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (1987), "a claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference. Further, as held by the Federal Circuit in *In re Bond*, 910 F.2d 831, 15 USPQ2d 1566 (1990), the elements must be arranged as required by the claim.

**2. Elements of the pending claims**

Pending claim 34, from which all other pending claims ultimately depend, is drawn to a method of producing and administering a prodrug complex. In this method, a drug is identified. A synthetic receptor is then selected that

specifically binds the drug via a saturable, noncovalent interaction between the drug and the synthetic receptor that can be competitively inhibited by structural analogs of the drug. This synthetic receptor is selected from the group consisting of antibodies, antibody fragments, oligonucleotides and oligosaccharides. The identified drug is then specifically bound to the selected synthetic receptor and the resulting prodrug complex is administered to an organism.

**3. The teachings of Morgan Jr. et al. (U.S. Patent 5,106,951)**

Morgan Jr. et al. (U.S. Patent 5,106,951) discloses a three-part complex requiring (a) an antibody; (b) a csDBM; and (c) a drug conjugate, wherein the csDBM is defined as a class of chemicals designed to fit the drug by combining multiple non-covalent interactions between functional groups on the drug and opposing functional groups on the csDBM (see Abstract). As taught at col. 4, lines 61-67 of the '951 patent, the immunoconjugates of Morgan Jr. et al. comprise a targeting protein such as an antibody or antibody fragment, a moiety termed a drug binding molecule of complementary structure (abbreviated csDBM) that is covalently bound to the antibody or carrier, and a drug noncovalently complexed to the csDBM. In another configuration, as taught at col. 4, line 67, through col. 5, line 2, the drug is first bound through covalent bonds to an antibody or carrier and then complexed

with a csDBM. The csDBM is further defined at col. 5, line 64 through col. 6, line 17, as a molecule that has a form opposite and complementary to that of a drug or has functionalities that are opposite and complementary in structure to a drug molecule. A preferred example is taught where the csDBM and the drug have a similar planar ring structure, but with opposing functionalities. Examples of opposing functionalities on the csDBM include groups for hydrogen and ionic binding and other noncovalent interactions, with or without electron poor or electron rich groups on the csDBM to increase the pi binding. It is also taught at this section that the csDBM is sterically oriented in proper three-dimensional alignment such that the functional group on the drug interacts with the opposing functional group on the csDBM in proper steric orientation.

**4. Elements of the Claimed Invention not taught by Morgan Jr. et al.**

The claimed invention requires that the selected synthetic receptor specifically binds the drug via a saturable, noncovalent interaction between the drug and the synthetic receptor that can be competitively inhibited by structural analogs of the drug. Further, the claims require the synthetic receptor to be selected from a specific group, namely a group consisting of antibodies, antibody fragments, oligonucleotides and oligosaccharides. Thus, as made clear in the pending claims, no moiety termed a drug

binding molecule of complementary structure (abbreviated csDBM) is involved in this specific binding of the identified drug to the selected synthetic receptor.

Morgan Jr. et al. Do not teach a synthetic receptor selected from the group consisting of antibodies, antibody fragments, oligonucleotides and oligosaccharides that specifically binds an identified drug. Thus, Morgan Jr. et al. do not teach all the elements of the claimed invention.

**5. The csDBM-antibody of Morgan Jr. et al. is not an antibody fragment**

Further, the Examiner's suggestion that the antibody-csDBM of Morgan meets the "antibody fragment" limitation of claims 34, 35, 36, 37, 38, 39 and 40 is inconsistent with the interpretation of the term "antibody fragment" taught not only by leaders in the antibody field but also by Morgan Jr. et al. itself.

Appellants are well aware that during patent examination the pending claims must be given the broadest reasonable interpretation consistent with the specification. However, both the MPEP 2111 and the Court of Appeals for the Federal Circuit in In re Cortright, 165 F.3d 1353, 1359, 49 USPQ 2d 1464, 1468 (1999) require that the broadest reasonable interpretation must also be consistent with the interpretation that those skilled in the art would reach. MPEP § 2111.01 requires that the words of a claim must be given their "plain meaning" unless they are defined in the specification. "In

other words, they must be read as they would be interpreted by those of ordinary skill in the art." See MPEP § 2111.01 and In re Sneed, 710 F.2d 1544, 218 USPQ 385 (Fed. Cir. 1983).

The term "antibody fragment" is not defined in the instant specification because it is a term of art defined by industry leaders in references such as U.S. Patent 5,855,577 and U.S. Patent 4,741,900.

U.S. Patent 5,855,577 teaches that antibody fragments contain the idiotype or antigen binding region of the molecule and can be generated by known techniques. As taught therein, such fragments include, but are not limited to, the F(ab')2 fragment which can be produced by pepsin digestion of the antibody molecule; the Fab' fragments which can be generated by reducing the disulfide bridges of the F(ab')2 fragment, and the 2 Fab or Fab fragments which can be generated by treating the antibody molecule with papain and a reducing agent.

U.S. 4,741,900 teaches that Fab' fragments of IgG immunoglobulins are obtained by cleaving the antibody molecule with pepsin (resulting in a bivalent fragment, $(Fab')_2$) or with papain (resulting in 2 univalent fragments, 2 Fab). The bivalent $(Fab')_2$ fragment can be split by mild reduction of one or a few disulfide bonds to yield univalent Fab' fragments. U.S. Patent 4,741,900 also teaches that Fab and $(Fab')_2$ fragments are smaller than a

whole antibody molecule and, therefore, permeate the target site or tissue more easily.

Further, and more importantly, Morgan Jr. et al. itself teaches at col. 7, lines 12-15, that antibody fragments include Fab, F(ab')2 and Fab'.

Interpretation of the antibody-csDBM of Morgan to meet the "antibody fragment" limitation of claims 34, 35, 36, 37, 38, 39 and 40 is also clearly inconsistent with teachings in Morgan Jr. et al. of embodiments involving a conjugate comprising an antibody fragment as the targeting protein, a csDBM moiety, and a drug. See, for example col. 4, lines 61-67, of Morgan Jr. et al. Clearly, binding of the csDBM moiety to an antibody fragment would not be taught by Morgan Jr. et al. if the term antibody fragment was meant to already encompass the csDBM.

Therefore, the entire basis for this rejection under 35 U.S.C. § 102(b) is flawed, as it relies upon an interpretation of the term antibody fragment inconsistent not only with the interpretation of those skilled in the art but also with the teachings of the cited prior art reference.

**B. Rejection of claims 34, 35, 36, 37, 38, 39 and 40 under 35 U.S.C. § 103(a) over Morgan Jr. et al. (U.S. Patent 5,106,951).**

Claims 34, 35, 36, 37, 38, 39 and 40 also stand rejected as being unpatentable under 35 U.S.C. § 103(a) over Morgan Jr. et al.

(U.S. Patent 5,106,951). In this rejection, the Examiner reiterates the suggestion that the antibody-csDBM of Morgan Jr. et al. meets the "antibody-fragment" limitation of the instant claims, since no language excluding the csDBM of Morgan Jr. et al. is included in the claims.

Appellant respectfully disagrees.

**1. Three basic criteria of *prima facie* obviousness**

In accordance with MPEP § 2143, to establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the reference itself or in the knowledge generally available to one of ordinary skill in the art, to modify the reference. Second, there must be a reasonable expectation of success. Finally, the prior art must teach or suggest all of the claim limitations.

**2. Morgan Jr. et al. provides no motivation or suggestion to produce the claimed invention**

As discussed in Section A(4) the pending claims of the instant application make clear that no moiety termed a drug binding molecule of complementary structure (abbreviated csDBM) is involved in this specific binding of the selected drug to the identified synthetic receptor.

In contrast, Morgan Jr. et al. state at col. 7, lines 31-39, that the:

> invention is a csDBM, a csDBM/drug complex, a carrier csDBM/drug conjugate, a targeting protein/csDBM/drug conjugate, a targeting protein/carrier/csDBM/drug conjugate, a targeting protein/carrier/drug/csDBM complex and a method of designing or producing a csDBM wherein a csDBM can be identified in nature or synthesized that will undergo multiple, non-covalent interactions with a drug.

Thus, quite clearly the csDBM is a required element of the invention of Morgan Jr. et al.

Removal of the csDBM element, as would be required for a synthetic receptor selected from the group consisting of antibodies, antibody fragments, oligonucleotides and oligosaccharides to specifically bind a drug via a saturable, noncovalent interaction between the drug and the synthetic receptor that can be competitively inhibited by structural analogs of the drug as claimed in the present invention, would clearly change the principle of operation of the immunoconjugate of Morgan Jr. et al. Thus, in accordance with MPEP § 2143.01 and the holding of the Court in *In re Ratti*, 270 F.2d 810, 123 USPQ 349 (CCPA 1959), the teachings of this reference provide insufficient motivation to render the claim *prima facie* obvious.

**3. Morgan Jr. et al. does not teach or suggest all claim limitations**

Morgan Jr. et al. do not teach or suggest specific binding of a drug directly to a synthetic receptor selected from the group consisting of antibodies, antibody fragments, oligonucleotides and oligosaccharides. Further, as discussed in detail in Section A(5),

the Examiner's suggestion that the antibody-csDBM of Morgan Jr. et al. meets the antibody fragment limitation of the instant claims is inconsistent with the interpretation of the term "antibody fragment" not only by those skilled in the art but also by Morgan Jr. et al.

Morgan Jr. et al. explicitly teaches embodiments of their immunoconjugate that includes an (unfragmented) antibody fragment covalently bound to a csDBM. Clearly such teachings are not suggestive of an antibody fragment comprising an antibody bound to a csDBM.

Thus, Morgan Jr. et al. also fails to teach or suggest all the limitations of the instant claimed invention.

**IX. Conclusion**

Because Morgan Jr. et al. fail to teach all the elements of the claimed invention as required to render the instant invention anticipated under 35 U.S.C. 102(b), and the reference does not meet the basic criteria required to render the instant invention obvious under 35 U.S.C. 103(a), reconsideration and withdrawal of the pending rejections of claims 34, 35, 36, 37, 38, 39 and 40 under 35 U.S.C. 102(b) and 103(a) is respectfully requested.

## X. Communications between Appellant and Examiner subsequent to the Final Rejection of July 16, 2002 and the Amendment of October 16, 2002

Appellant's attempt in the amendment of October 16, 2002 to delete the term "antibody fragment" to facilitate prosecution of the instant case and gain allowance of claims to at least a portion of his invention was denied entry in Advisory Actions dated December 3, 2002 and January 27, 2003. Appellant respectfully submits that since this term was a part of a markush group the entire listing should have already been searched by the Examiner after submission of the claims in November of 2001 and election of this group of claims in following restriction in March of 2002. However, the Examiner advised that deletion of this phrase would require further searching.

Upon request of Examiner Stanton, the Examiner of record reviewed the pending claims (still inclusive of the phrase antibody fragment) and proposed amendment of the transitional phrase of method claim 34 to "consisting of". While Appellant gave consideration to this amendment, such limitation is undesirable as further method steps can be conducted as evidenced by dependent claim 35.

However, Appellant proposed amending the claims to specify that the prodrug complex formed consisted essentially of the identified drug specifically bound to the synthetic receptor. The

proposed claims could not be fully considered by the Examiner of record due to time constraints on the Examiner.

Accordingly Appellant is providing herewith a copy of the proposed claims in Appendix II and consideration of the allowability of these claims by the Board is respectfully requested should the pending claims of Appendix I not be deemed allowable.

Respectfully submitted,

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